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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,795	04/23/2001	Erin E. Murphy	SF0818KQ	5250

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EXAMINER	
O HARA, EILEEN B	
ART UNIT	**PAPER NUMBER**
1646	13

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/840,795	Applicant(s) MURPHY ET AL.	
	Examiner Eileen O'Hara	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *11-15,21 and 22* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Claims 11-15, 21 and 22 are pending in the instant application. Claims 11, 12 and 15 have been amended, claims 1-10 and 16-20 have been canceled and claims 21 and 22 have been added as requested by Applicant in Paper Number 11, filed May 5, 2003.

Priority

2. Applicants' amendment to the specification to update the priority claimed in the declaration is acknowledged.

Specification

3.1 The objection to the specification is maintained because Although Applicants state that they have deleted the Table on page 7 of the response, there was no amendment requesting the deletion. In addition, Tables 1 and 2 should also be deleted, since they are also sequence listings.

3.2 The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Withdrawn Objections and Rejections

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Response to Amendment

5. The declaration under 37 CFR 1.132 filed May 13, 2003 is insufficient to overcome the rejection of claims 11-15, 21 and 22 based upon lack of utility under 35 USC § 101 and § 112 as set forth in the last Office action because: the declaration fails to provide support for the claimed invention having either a specific and substantial asserted utility or a well established utility, discussed in detail below under the rejection under 35 USC § 101 and § 112.

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 11-15 remain rejected, and new claims 21 and 22 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous Office Action, Paper No. 8, at pages 4-7, and below.

Applicants traverse the rejection and assert on page 8 of the response that the specification provides at least one specific, substantial and credible utility based on the sequence homology to existing members of the TNF receptor family and the expression of RANKL (RANK like) in inflammatory responses. Applicants note that according to the Utility Examination Guidelines "[w]hen a ... [protein] is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial and credible utility to the assigned protein. Applicants assert that the specification also discloses the expression of

RANKL in inflammatory responses, and that under the known, specific substantial, and credible utility known for the TNF receptor family members, particularly for inflammatory and allergic responses and associated diseases, this is sufficient to meet the standard under 35 U.S.C. §§ 101 and 112. As examples, Applicants point to page 57 of the specification, which clearly states that antibodies to RANKL should be useful in the treatment of conditions associated with abnormal physiology or development, including proliferation, and cites modulation of the development of lymphoid cells in particular, that RANKL plays a role in regulation or development of hematopoietic cells, lymphoid cells, which affect immunological responses. Applicants also point to page 30 of the specification which discloses increased expression of RANKL in lungs of allergic guinea pigs compared to normal lungs, and a similar result with allergic monkey lung. Applicants further submit the declaration of Ms. Jeanine Mattson, which supplies data showing that real time PCR analysis showed that detectable expression of SEQ ID NO: 17 was not observed in control human or C. macaque lung, but that lung with idiopathic pulmonary fibrosis showed a greater than 20 fold increase in expression level compared to the control lung, and in the C. macaque samples, lung samples taken 24 hours post-challenge with Ascaris had a greater than 9 fold increase in SEQ ID NO: 17 expression (Tables 1 and 2 of declaration). Applicants further assert that as shown in Exhibits A and B, the abnormal proliferation of hematopoietic cells are a cause of the pathology observed in the human state, and that RANKL is a member of the TNF receptor superfamily, a well-defined cytokine receptor family known to participate in the regulation of hematopoiteic cell proliferation and viability, and therefore the skilled artisan would recognize and believe the utilities disclosed in the instant application and thus meet the utility requirement.

Applicants' arguments have been fully considered but are not deemed persuasive. Although a correlation may exist between expression of the nucleic acids of the instant invention and pulmonary inflammation is not sufficient guidance to use the claimed antibodies (or nucleic acids or polypeptides); it merely defines a starting point for further research and investigation. Although homology to the TNF receptor family and expression provides some evidence that the claimed protein is a member of the TNF receptor superfamily, it is not predictable what the function of the proteins of the instant invention are from this information. Whereas a broad class of enzyme such as the ligases have a general utility in such an application as ligation of DNA for cloning purposes and which is essentially applicable to all of the members of that class, the class of proteins known as TNF receptors do not have a common practical utility which is based upon a property common to all of the members of that class. Members of this superfamily bind to a large variety of different ligands, mediates different signals, are expressed in different cell types and modulate different physiological processes, and are involved in different diseases and/or disorders, and it is not predictable what the specific physiological function of a TNF receptor is based on homology to other members of this family (Wallach, D. (2000) TNF ligand and TNF/NGF receptor families. In: Cytokine Reference (Joost J. Oppenheim and Marc Feldmann editors in chief, Academic Press (London), 377-411). Though the protein of the instant invention may be classified as a member of the TNF receptor superfamily, this does not automatically confer a specific and substantial utility to the protein, since there is diversity in the activities and biological functions of these receptors.

Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001, where on page 1096, third column, it is stated:

> "For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class."

The receptors of RANKL fall into this category.

The proposed use of the claimed invention is simply a starting point for further research and investigation into practical uses of the protein. This further experimentation is a useful in basic research, but does not constitute a specific, substantial or well-established utility.

As the Supreme Court said in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct. 1966):

> "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

It is not known or disclosed if increased expression of the nucleic acids in pulmonary disorders is caused by or results from this expression, and one of ordinary skill in the art would not know how to use the molecules of the instant invention except for further research to discover it's role in inflammation. At least one specific and substantial activity must be disclosed. The Revised Interim Utility Guidelines Training Materials state "Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities." The polypeptides of the instant invention would require substantial further research to determine how they were involved in any disease state.

As further evidence that function cannot be predicted from identification of a protein as a member of a protein family, Yan et al., (cited in Paper No. 8, pages 8-9), discloses a polypeptide identified as human XEDAR (Fig. 1A) which is 99.5% identical to amino acids 1-205 of the

polypeptide of SEQ ID NO: 19 (primate RANKL) of the present application, which is 231 amino acids in length, and has one conservative mismatch at amino acid 57. The protein of Yan et al. is 297 amino acids in length, which indicates that the proteins of Yan et al. and SEQ ID NO: 19 of the instant application are probably orthologs and/or splice variants of the same protein. Yan et al. teach that the XEDAR protein is a receptor in the TNF family of receptors, and binds the ligand EDA-A2, which has been shown to be involved in hypohidrotic (anhidrotic) ectodermal dysplasia (EDA), a disorder characterized by the abnormal development of hair, teeth and eccrine sweat glands, and that mutations in the X-linked EDA gene, a distantly related member of the TNF-ligand superfamily, are responsible for most of the clinical cases studied to date (page 524, first column first and second full paragraphs). Yan et al. demonstrated that cells transformed with XEDAR and exposed to EDA-A2 activated the transcription factor NK-κB, and that the cytoplasmic region of XEDAR bound TRAF1, TRAF3 and TRAF6 (page 524, third column, paragraph bridging pages 524-525). Yan et al. examined expression of XEDAR in developing mouse skin and found that XEDAR expression by E16 and E17(embryonic day 16 and 17) was found in large amounts in the maturing hair follicles, and by postnatal day 1 (P1) was mainly confined to hair follicles (page 525, columns 2 and 3, Fig. 4B). EDA-A2 expression was found to be more concentrated in the central core of the developing hair follicle compared to EDA-A1 (splice variant of EDA-A2 that binds EDAR, a different but related receptor to XEDAR), whereas EDA-A1 expression was circumferential (paragraph bridging pages 525 and 526). In a skin organ culture system, EDA-A2 increased the number of epidermal invaginations that are a precursor stage to mature hair follicles (page 526, column 1). In summary, on page 526, middle column, Yan et al. state:

"Members of the TNFR family are important in immunity and inflammation. Our study indicates that involvement of this family in morphogenesis."

Yan et al. al is evidence that even though proteins may be members of a receptor family, in this instance the TNF receptor family, it is not predictive what the functions or activities of such a family member is. For these reasons and those of record in the previous Office Actions, the rejection under 35 USC § 101 is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11-15 also remain rejected and new claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record in the previous Office Action, Paper No. 8, at page 7. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Effective Priority Date

35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

8. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because the instant application does not meet the requirements of 35 U.S.C. § 112, first paragraph, for those reasons given above and it is a continuation of application Serial Number 09/351,777, the prior provisional applications do not meet those requirements and, therefore, are unavailable under 35 U.S.C. § 119(e). The effective priority date of the instant application is considered to be the filing date of the parent application 09/351,777, July 12, 1999, because the claimed invention is not supported by either a specific and substantial utility or a well established utility.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 11-14, 21 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Goddard et al., U.S. published application 20030092044, effective filing date April 12, 1999 (60/128,849).

Claims 11-15, 21 and 22 encompass binding compounds comprising an antibody binding site which specifically binds and is immunoreactive to at least 17 contiguous amino acids from the signal processed form of SEQ ID NOS: 15, 17 or 19, wherein the binding compound is an

antibody molecule which may be a monoclonal or humanized antibody, present in a polyclonal antiserum, detectably labeled, sterile or in a buffered composition, and methods of using the binding compound to form a binding compound:antigen complex in a human biological sample.

Goddard et al. discloses an amino acid sequence (SEQ ID NO: 6) that is 99.5% identical to amino acids 1-205 of SEQ ID NO: 19 of the instant specification, and comprises at least 17 contiguous amino acids of the signal processed form of SEQ ID NOS: 15 and 17. Goddard et al. also teach antibodies to the protein, which may be a monoclonal or humanized antibody, present in a polyclonal antiserum, detectably labeled, sterile or in a buffered composition, and methods of using the binding compound to form a binding compound:antigen complex in a human biological sample (sections 0005, 0027, 0028, 0034, 0072, 0173 and 0210). Therefore, the binding compounds of Goddard et al. anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goddard et al., U.S. published application 20030092044, and further in view of Akita et al., US Patent No. 5,968,511. Claim 15 encompasses the binding compound of claim 12 in a kit with instructions.

The teachings of Goddard et al. are described above. Goddard et al. does not teach the binding compounds in a kit with instructions.

Akita et al. teach a kit comprising antibody and instructions for use (claim 17).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use antibody binding compounds of Goddard et al., a put them in a kit with instructions, as taught by Akita et al. The skilled artisan would be motivated to do so in order to use the antibody to detect protein in a biological or tissue sample in order to determine where the protein was present, and there would be a reasonable expectation of success, since antibody kits with instructions have been widely and successfully used in the field of biochemistry.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner

LORRAINE SPECTOR
PRIMARY EXAMINER